Pharmaceutical Research, Vol. 19, No. 12, November 2002 (© 2002)

Review Article

β-Adrenergic Receptor Polymorphisms: Cardiovascular Disease Associations and Pharmacogenetics

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Received July 13, 2002; accepted September 6, 2002

The β-adrenergic receptors (βAR) play important roles in cardiovascular function and disease, and both agonists and antagonists are widely used in various settings for treatment of cardiovascular disease. Both the β_1AR and β_2AR genes have several polymorphisms that are common in the population and result in encoding of different amino acids. More importantly, *in vitro* functional studies suggest that these polymorphisms have functional significance. In this review we summarize the literature on the relationship between the βAR polymorphisms and cardiovascular disease as well as the literature on the impact of these polymorphisms on drug response. Additionally, the polymorphisms in both the β_1AR and β_2AR genes are in linkage disequilibrium; thus, the relevance of single polymorphism vs. haplotype analysis is discussed. Further study of the βAR genetic polymorphisms is likely to enhance our understanding of cardiovascular disease and improve our use of β-agonists and β-antagonists in treatment of cardiovascular disease.

KEY WORDS: β_1-adrenergic receptor; β_2-adrenergic receptor; genetic polymorphisms; haplotype; cardiovascular disease.

INTRODUCTION

The β-adrenergic receptors (βARs) are G_s protein–coupled receptors that play important roles in cardiovascular function and disease, through serving as receptors for the neurohormones norepinephrine and epinephrine. In the myocardium, stimulation of β_1- and β_2ARs leads to positive inotropic and chronotropic activities. β_1ARs predominate in the heart, representing about 80% of the myocardial βARs; thus, they tend to be viewed as the more important of the βARs with respect to the cardiovascular system. β_1- and β_2ARs in the kidneys stimulate the release of renin, thereby playing a role in activation of the renin-angiotensin-aldosterone system. β_2ARs are also located in arteries, where their stimulation leads to vasodilation. The β_3AR was more recently recognized, with primary roles believed to be metabolic in nature, although there is some evidence that they may have negative inotropic effects in the heart (1).

The role of the βARs in cardiovascular function and disease is also highlighted by the important roles of drugs whose actions are based on binding to the βARs. β-Agonists, such as dobutamine, dopamine, and isoproterenol, are used acutely in support of the failing heart. More important are the β-blockers, which represent first line therapy for the management of chronic heart failure, hypertension, acute and postmyocardial infarction patients, chronic stable angina, and unstable angina (2–6). They are also commonly used for control of symptoms in atrial fibrillation and other arrhythmias (7). There are no cardiovascular drugs that have a wider range of indications than β-blockers, making them a critical drug class for the management of cardiovascular disease. The breadth of uses for β-blockers also suggests that activation of the βARs, or the sympathetic nervous system (SNS), plays an important role in most cardiovascular diseases. The fact that β_1AR-selective antagonists are equivalent to nonselective blockers in essentially all situations provides additional evidence that the β_1ARs are the more important β-receptors with respect to cardiovascular disease.

The purpose of this review is to provide an overview of the potential contributions of genetic variability in the βARs to cardiovascular disease and the impact of this variability on drug response. The β_1AR polymorphisms were identified much more recently (1999) than the β_2AR polymorphisms (1993) (8,9). Thus, the literature on the β_1AR polymorphisms is somewhat more limited than for the β_2AR polymorphisms. However, it is anticipated that within the next couple of years, the literature on the β_1AR polymorphisms will grow exponentially.

β_1-ADRENERGIC RECEPTORS

Genetic Polymorphisms

The β_1AR is encoded by an intronless gene located on chromosome 10q24-26. Like all G-protein-coupled receptors,

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ABBREVIATIONS: βAR, β-adrenergic receptor; DSE, dobutamine stress echocardiography; FEV_1, forced expiratory volume in 1 s; 5′LC, 5′ leader cistron; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism; SNS, sympathetic nervous system.

the β_1AR contains an extracellular amino terminus, seven transmembrane spanning regions, and an intracellular carboxy terminus. Genetic polymorphisms of the β_1AR at codons 49 and 389 were first reported in 1999 (9). Since then, another group has reported an additional 12 single-nucleotide polymorphisms (SNPs), five of which are nonsynonymous (10). The nonsynonymous genetic polymorphisms of the β_1AR and their allele frequencies are summarized in Table I, and their locations are highlighted in Fig. 1. Two of the nonsynonymous SNPs are located in the amino terminus, at codons 49 and 59 (10). The remaining five SNPs are located in the carboxy terminus, which means that the transmembrane spanning region is highly conserved. The carboxy-terminus SNPs are located at codons 389, 399, 402, 404, and 418 (10). The codon 49 and 389 SNPs have been the most commonly studied because they both have allele frequencies greater than 10%. It should be noted that the remaining polymorphisms of the β_1AR have been reported by a single group, and it is possible that as other resequencing efforts on the β_1AR are completed, not all of these sites will, in the end, be judged polymorphic.

Although most genetic association studies have focused on a single polymorphism, there is increasing interest in haplotype. We recently tested for linkage disequilibrium (LD) between the codon 49 and 389 SNPs in nearly 700 women and found there was significant linkage disequilibrium between these two SNPs (11). Only three of the possible four haplotypes were found among the 1,254 alleles for which we could assign haplotype. Despite being the predicted haplotype for 52 alleles, Gly^{49}/Gly^{389} was never observed. Thus, it is possible to assign haplotype for the β_1AR with confidence, even in double heterozygotes. The frequencies of the three observed haplotypes in Caucasians and African Americans are shown in Table II. Whether analysis of data by haplotype will be more informative than analysis of either SNP alone is currently under investigation.

Functional Consequences of β_1AR Polymorphisms

In vitro functional studies have been conducted for both of the common β_1AR SNPs. Rathz *et al.* recently reported on the functional consequences of the codon 49 polymorphism after using site-directed mutagenesis techniques (12). The investigators found that the polymorphism had no effect on ligand binding, coupling efficiency to G_s protein, or agonist-promoted internalization. They did find, however, that the polymorphism was associated with differences in agonist-promoted receptor down-regulation. Specifically, long-term agonist exposure resulted in slight increases in receptor density for the Ser^{49} form of the receptor and approximately 25% down-regulation of the Gly^{49} form. Further studies suggested that the mechanism underlying this difference is enhanced receptor degradation in the presence of agonist by the Gly^{49} form. These data are not surprising, given the location of the polymorphism, and suggest the Ser^{49} form of the receptor might have higher receptor expression levels, particularly in diseases in which there is increased SNS activation, such as heart failure.

Site-directed mutagenesis studies of the codon 389 polymorphism also provided interesting insight into the functional effects of this polymorphism, with findings that have been supported by several subsequent studies in humans. Mason *et al.* (13) found that basal adenylyl cyclase activity was almost twofold higher for the Arg^{389} receptor form than the Gly^{389} form, and maximal agonist-stimulated adenylyl cyclase activity was about threefold higher for the Arg^{389} form. Further experiments revealed that these differences reflected increased coupling to G_s by the Arg^{389} form. This finding was not surprising, given that the region of the polymorphism is known to be important for coupling of receptors to their G protein.

Table I. Nonsynonymous β_1AR Genetic Polymorphisms and Allele Frequencies

Nucleotide substitution	Amino acid substitution	Allele frequency of variant		
		Caucasians	Asians	African Americans
A145G	$Ser^{49}Gly$	0.15[a]	0.15[b]	0.29[c]
G175T[e]	$Ala^{59}Ser$	0.04[d]	NR	NR
C1165G	$Arg^{389}Gly$	0.27[a]	0.27[b]	0.42[a]
C1195T[e]	$Arg^{399}Cys$	0.013[d]	NR	NR
A1205G[e]	$His^{402}Arg$	0.013[d]	NR	NR
A1210G[e]	$Thr^{404}Ala$	0.013[d]	NR	NR
C1252G[e]	$Pro^{418}Ala$	0.013[d]	NR	NR

[a] Compiled from various sources (10,11,17,58).
[b] From Moore *et al.* (58).
[c] From Terra *et al.* (11).
[d] From Podlowski *et al.* (10).
[e] It should be noted that these SNPs have been reported by one group only; thus, future resequencing efforts could reveal these sites to be nonpolymorphic.

Associations of β_1AR Polymorphisms with Cardiovascular Function and Disease

Resting and Exercise Hemodynamics and Hypertension

Several different studies have investigated the effects of the β_1AR genetic polymorphisms on resting hemodynamics and hypertension/blood pressure. Perhaps the best designed of these studies was a hypertension association study from Sweden (14). This study included both a case-control association study and a sib-pair family study of hypertension. Both study approaches revealed an association between Arg^{389} homozygous genotype ($Arg^{389}Arg$) and blood pressure/hypertension. Furthermore, the Arg^{389} homozygous genotype was associated with a significantly higher resting heart rate. They found no association between codon 49 genotype and blood pressure, heart rate, or presence of hypertension. The findings from this study would be viewed as highly consistent with the *in vitro* data on the codon 389 polymorphism. They could also be considered consistent with the codon 49 *in vitro* data because increased levels of SNS activation might be needed to see any functional consequences of this polymorphism.

Consistent with the study from Sweden, we recently reported that in a population of 142 β-blocker-free patients undergoing cardiac testing, codon 389 genotype was significantly associated with resting hemodynamics. The population studied was patients with a clinical indication for dobutamine stress echocardiography (most commonly to evaluate symptoms of chest pain or need for cardiovascular clearance for surgery). Patients undergoing this testing have a minimum

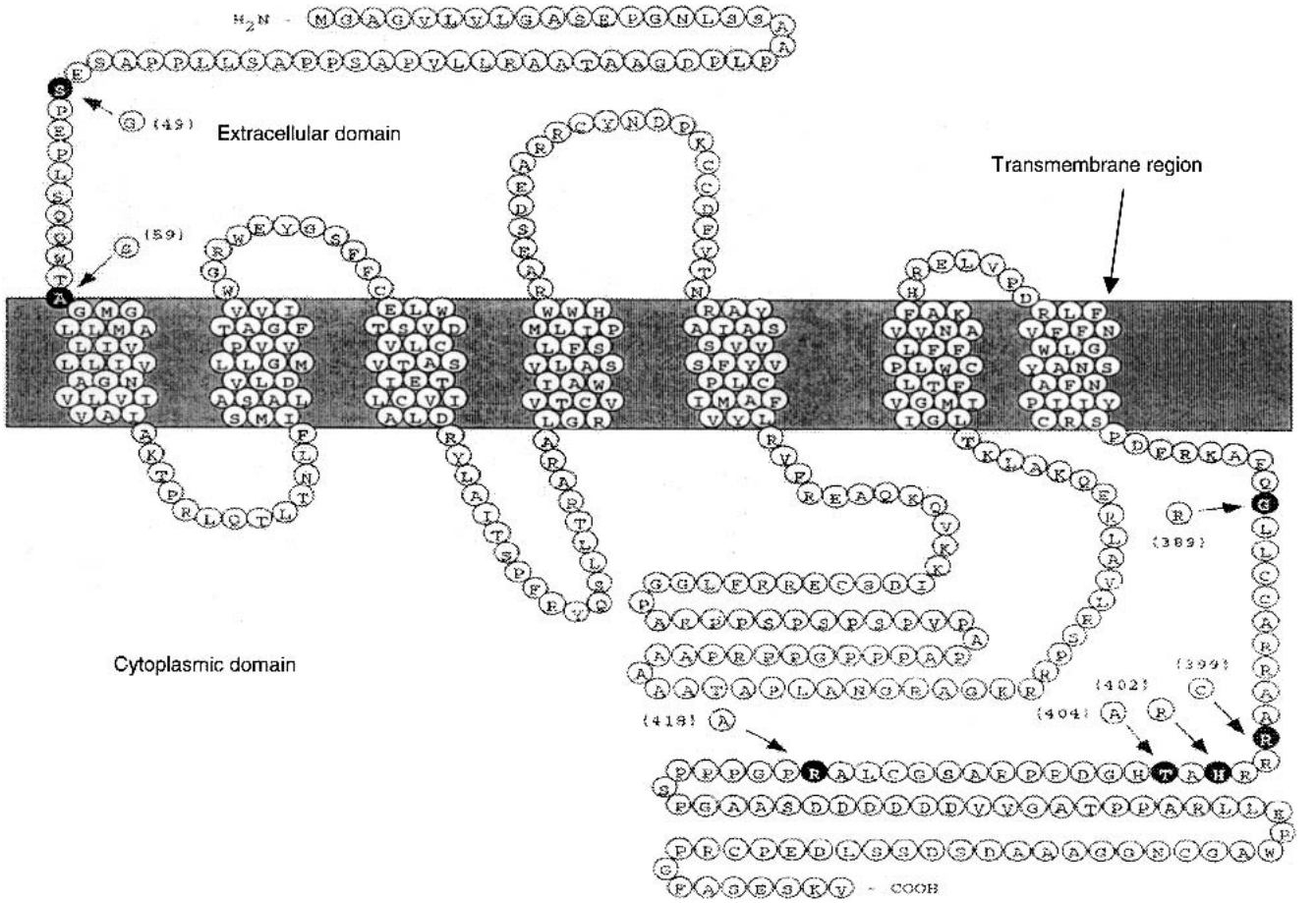

Fig. 1. The β_1-adrenergic receptor. Schematic representation of the amino acid sequence of the β_1AR, highlighting the genetic polymorphisms that result in different amino acids.

30-min supine rest period, and hemodynamic measurements were made at the end of this period. Patients were balanced between genotype groups for demographic factors, including hypertension, diabetes, body mass index, race, gender, and drugs being taken at the time of study. Patients on β-blockers were excluded from the analysis. In this population we found that those with the Arg^{389} homozygous genotype had significantly higher resting heart rates and diastolic blood pressures than carriers of the Gly^{389} allele (heart rate: 78 ± 11 bpm vs. 72 ± 12 bpm, p = 0.001; DBP: 81 ± 11 mmHg vs. 76 ± 13 mmHg, p = 0.008) (15). When Caucasians were evaluated alone, the differences were more striking, with systolic blood pressure also revealing differences by genotype. We found no differences in resting hemodynamics based on codon 49 genotype. In contrast to the findings from these two studies is a study of Chinese and Japanese families in which $Ser^{49}Ser$ was associated with significantly higher resting heart rates (16). Resting heart rate was not associated with codon 389 genotype, and blood pressure or hypertension status was not associated with β_1AR genotype at either codon. This study was comprised of hypertensives (73%) and individuals with low normal blood pressure, and 88% of the hypertensives were on antihypertensive drugs, the most common of which were β-blockers. The high degree of antihypertensive drug use, particularly β-blockers, presents a potential for confounding of both heart rate and blood pressure data. Although the authors attempted to deal with these issues in their statistical analysis, it is difficult to interpret these data with a high degree of confidence.

Table II. Observed β_1AR Haplotypes in Caucasian and African American Women[a]

Haplotype nucleotides	Amino acids	Frequency in Caucasians	Frequency in African Americans
AC	Ser^{49}/Arg^{389}	0.65	0.42
AG	Ser^{49}/Gly^{389}	0.26	0.36
GC	Gly^{49}/Arg^{389}	0.09	0.22
GG	Gly^{49}/Gly^{389}	0	0

[a] From Terra et al. (11).

The association of the codon 389 polymorphisms with exercise hemodynamics has also been investigated in two similarly designed studies conducted by different groups (17,18). Both studies included small numbers (<25 study subjects) of young, healthy volunteers, with similar distributions of individuals who were Arg^{389} and Gly^{389} homozygotes. The investigators from both groups found no differences in resting or exercise heart rate based on codon 389 genotype.

Thus, a consistent message on the relationship between the β_1AR polymorphisms and hemodynamics does not emerge from these studies. Clearly the best designed study is that of Bengtsson *et al.* (14), whose findings are consistent with the *in vitro* data and the study from our laboratory. The

findings of Bengtsson *et al.* (14) are also consistent with our recent finding of an association between antihypertensive response to β-blockers and β_1AR genotype (*vide infra*). The other studies had certain limitations, such as small sample size or confounding by drug therapy. Additionally, the influence of age, race/ethnicity, and presence or absence of disease on the functional consequences of the β_1AR polymorphisms remains to be determined.

Heart Failure

Heart failure is a disease process associated with marked SNS activation and for which long-term stimulation of the β-adrenergic receptors is detrimental. Additionally, β-blockers represent first-line therapy for heart failure. Thus, there is great interest in the potential impact of the β_1AR polymorphisms on heart failure.

Heart failure is a clinical syndrome that results from numerous other diseases, most commonly ischemic heart disease and hypertension. Thus, one would not expect the β_1AR polymorphisms to be associated with the presence or absence of heart failure. Consistent with this expectation are data suggesting no differences in β_1AR allele frequencies between heart failure patients and controls for either codon 49 (19) or 389 (20).The only study reporting differences in allele frequencies between cases and controls is somewhat suspect because the reported allele frequency of the codon 49 polymorphism for controls is highly inconsistent with all other reports of the allele frequency of this polymorphism (10).

Of greater interest is the potential impact of the genetic polymorphisms on heart failure prognosis and outcomes. The only study to date to undertake such an analysis reported that after 5 years of follow-up, patients with the Ser^{49} homozygous genotype were significantly more likely than Gly^{389} carriers to have been hospitalized for heart failure, undergone heart transplantation, or died (19). These findings are particularly intriguing in that they are entirely consistent with the *in vitro* data for codon 49. Although these investigators did not investigate the codon 389 polymorphism, one could speculate that similar outcome differences could be observed with this polymorphism. These data provide a fascinating first look at the potential relationship between the β_1AR polymorphisms and prognosis in heart failure.

Pharmacogenetics

In the first prospective study of the association between β_1AR polymorphisms and β-blocker response in hypertensive patients, we recently reported on the antihypertensive effects of β-blockers by genotype. We found that Arg^{389} homozygotes had a significantly greater reduction in 24-h and daytime diastolic blood pressure than Gly^{389} carriers (21). And in multivariate regression analysis, we found that the significant predictors of blood pressure lowering with a β-blocker were baseline blood pressure, codon 389 genotype, and codon 49 genotype. Of interest was the fact that we saw no association between the codon 49 or 389 genotype and the negative chronotropic effects of β-blockers. Although these data need confirmation in larger and different populations, they are consistent with the *in vitro* functional studies and provide insight into the potential role of the β_1AR polymorphisms in β-blocker response.

Another group retrospectively studied the codon 389 genotype and β-blocker response and found no association (22). There are several potential explanations for why their retrospective findings were inconsistent with the data from our prospective study. The most likely explanations include study design issues, such as lack of dose titration to response and use of clinic (vs. 24-h) blood pressure recordings in their study. Both of these study design issues could have reduced their ability to measure the true blood pressure response to β-blockers.

The *in vitro* data for the codon 49 and 389 polymorphisms suggest there might also be differences in β-agonist response by genotype. We have recently completed a study of the relationship between β_1AR genotype and response to dobutamine during dobutamine stress echocardiography (DSE). The primary response measure during DSE is the increase in heart rate. We have found no association between codon 49 genotype and heart rate or blood pressure response to dobutamine. However, our data suggest there may be an association between the codon 389 genotype and response during DSE (unpublished data).

β-Blockers and, to a lesser extent, β-agonists are important agents for treatment of cardiovascular disease. More importantly, there is much interpatient variability in the responses to these drugs. The pharmacogenetics literature on β-blockers (and β-agonists when used in the cardiology setting) is admittedly limited at present. Nonetheless, there is great interest in unraveling the genetic basis for response to these drugs, with the ultimate goal of improving their utilization in the treatment of cardiovascular disease. Thus, there seems to be little question that many studies will be published in coming years on the role of the β_1AR and other polymorphisms in β-blocker and β-agonist responses.

β_2-ADRENERGIC RECEPTOR

Genetic Polymorphisms

The β_2AR is also encoded by an intronless gene, located on chromosome 5q31-32. It has long been recognized that the receptor is coupled to the stimulatory protein G_s (23), but more recent data also suggest the β_2AR couples to G_i (24). Immediately upstream from the coding region for the β_2AR is a 19–amino acid peptide, referred to as the 5′ leader cistron (5′LC), which is involved in receptor expression. To date, 11 polymorphisms have been reported for the β_2AR coding block, four of which change the encoded amino acid (codons 16, 27, 34, and 164) (25). The polymorphism at codon 34 ($Val^{34}Met$) occurs rarely and has not been shown to modify receptor function; thus, it is not discussed further (26). The 5′LC region contains nine polymorphisms, and one results in an amino acid change at codon –19($Cys^{-19}Arg$) (27). Average allele frequencies for the nonsynonymous β_2AR polymorphisms are listed in Table III.

The polymorphisms in the β_2AR gene display marked linkage disequilibrium (LD), such that Arg^{-19} essentially always occurs with Glu^{27}, and Arg^{16} rarely occurs with Arg^{-19} or Glu^{27}. Thus, considering the three common, nonsynonymous SNPs, the most common haplotypes are Arg^{-19}/Gly^{16}/Glu^{27} (RGE), Cys^{-19}/Gly^{16}/Gln^{27} (CGQ), and Cys^{-19}/Arg^{16}/Gln^{27} (CRQ) (28). In one study, a total of 13 SNPs (eight in the 5′LC region and 5 coding block) were used to study the

Table III. Ethnic Differences in β_2AR Allele Frequencies[a]

Polymorphism	Allele	Blacks	Whites	Asians
5′LCCys^{19}Arg	Arg^{-19}	0.21	0.35	0.08
Arg^{16}Gly	Arg^{16}	0.49	0.46	0.59
Gln^{27}Glu	Glu^{27}	0.20	0.35	0.07
Thr^{164}Ile	Ile^{164}	NR[b]	0.04	NR[b]

[a] Compiled from references 33, 35, and 47.
[b] Not reported.

association between β_2AR SNPs and haplotypes and the bronchodilatory response to albuterol (27). If these polymorphisms occurred randomly, one would expect 2^{13} or 8,192 haplotypes. However, only 12 haplotypes were identified (27). Furthermore, five haplotype pairs accounted for 90% of the population in this study. The degree of LD in the β_2-gene suggests that examination of haplotypes, rather than individual SNPs, may be more appropriate for disease association and pharmacogenetic studies.

Determination of haplotype requires knowledge of the genetic information on a single allele. Experimental determination of haplotype is typically difficult because of the distance between the polymorphisms. Thus, in the absence of family data, haplotypes are typically assigned using statistical algorithms, as was done by Drysdale *et al.* (27). However, because the β_2AR gene is intronless, (and thus relatively small), and the nonsynonymous SNPs are relatively close to one another, we were able to develop a method that allowed for experimental determination of the β_2AR haplotypes (28). This method relies on denaturation selective amplification, such that any allele containing Cys^{-19} is efficiently amplified at denaturation temperatures of either 94°C or 97°C, whereas an Arg^{-19}-containing allele undergoes efficient amplification only at 97°C (28). Thus, unlike most genes with multiple SNPs that are in linkage disequilibrium, it is relatively easy to experimentally determine β_2AR haplotypes.

Functional Consequences of β_2AR Polymorphisms

The functional effects of the β_2AR polymorphisms have been studied in several settings. Neither ligand binding nor adenylyl cyclase activity is altered by the presence of the codon 16 (Arg → Gly) or codon 27 (Gln → Glu) polymorphisms in the extracellular amino terminus of the β_2AR gene (29). However, much like the amino-terminus polymorphism of the β_1AR, these two polymorphisms influence receptor desensitization. *In vitro* studies with transfected cells and cell culture systems demonstrated that both the Arg^{16} and Glu^{27} forms of the receptor were resistant to agonist-promoted down-regulation (29,30). However, *in vitro* studies with human lung mast cells obtained from patients undergoing surgery revealed conflicting results with respect to the codon 16 polymorphism (31). In this study, mast cells expressing the Gly^{16} form of the β_2AR were resistant to agonist-induced down-regulation. The importance of these discordant results is magnified when one considers the degree of LD in the β_2AR. For example, nearly all subjects who are Glu^{27} homozygotes are also Gly^{16} homozygotes (32,33). Thus, the early *in vitro* studies in which Glu^{27} appeared to be resistant to agonist-promoted down-regulation are somewhat misleading because the haplotype in those experiments was Arg^{16}/Glu^{27}, a haplotype that is rare in nature (29). Because the LD between these two SNPs was not recognized at that time, the investigators would not have known that they were creating unrealistic haplotypes. Nonetheless, this example points out how study of polymorphisms in isolation, particularly with site-directed mutagenesis techniques, can result in spurious findings. Thus, the importance of examining β_2 haplotype cannot be overemphasized. A seminal paper found no association between individual β_2AR SNPs and response to albuterol. However, haplotype pair was significantly related to improvements in FEV_1 from albuterol (27). Therefore, examination of haplotypes resulted in the best prediction of therapeutic efficacy.

The fourth membrane-spanning domain contains a nonsynonymous SNP at codon 164 (Thr → Ile). The Ile^{164} form of the receptor displays threefold lower affinity for isoproterenol, epinephrine, and norepinephrine along with markedly depressed basal and agonist-stimulated adenylyl cyclase activity compared to the Thr^{164} form (34). Moreover, the Ile form of the receptor also down-regulates compared to the wild type (34).

Finally, a SNP at codon –19 of the 5′LC region results in an Arg → Cys substitution. Site-directed mutagenesis studies of the β_2AR 5′LC have shown that Cys^{-19} results in 72% higher β_2AR expression than the Arg^{-19} form (35). Consequently, the Cys^{-19} form of the 5′LC has higher isoproterenol-mediated activation of adenylyl cyclase (35).

Associations of β_2AR Polymorphisms with Cardiovascular Disease

A myriad of studies have investigated the association between β_2AR polymorphisms and the pathogenesis of cardiovascular disease. Although it is not the focus of this review, numerous studies have also investigated the association between β_2AR polymorphisms and the diagnosis of asthma, disease severity, and response to β_2 agonists (25,27,36,37).

Hypertension

An established etiology is absent for 95% of cases of hypertension (essential hypertension). However, it is believed that genetic factors account for up to 40% of the variability in blood pressure across the population (38). The β_2AR gene is a candidate gene for hypertension because blunted β-mediated vasodilation occurs in hypertensive patients (39). The literature examining the association between β_2AR polymorphisms and hypertension is laden with contradictory results. For example, some studies show an association of the Arg^{16} allele and hypertension (40–42). Conversely, other studies suggest that the Gly^{16} allele is associated with hypertension (43) or is associated with higher blood pressure levels (44,45). Still other studies demonstrate no association between codon 16 genotype and hypertension (46–48). The design and results of these studies are summarized in Table IV.

One of the largest and perhaps best designed β_2AR association studies comes from an analysis of the Rochester Heart Study (49). The genes of focus for this study were selected based on linkage analyses, and five genes in the chromosome 5 linkage region were selected. This study included 55 pedigrees with at least one sib pair discordant for systolic

Table IV. Hypertension Association Studies with the β_2AR Polymorphisms[a]

Sample size	Ethnicity	SNPs	Results	Hypertension phenotype
34	Norwegians	5′LC (–19), C16, C27	Arg^{16} allele associated with increased BP levels and significantly higher in HT offspring compared to NT offspring (58% vs. 28%, $p < 0.001$) (42)	Offspring of either 2 HT or 2 NT parents
291 HT without DM, 124 HT with DM, 265 healthy controls	Swedes	5′LC(–19), C16, C27	OR for HT in patients with type 2 DM was 2.14 (95% CI 1.05–4.33) for Arg^{16} homozygotes; siblings with ≥1 copy of the Arg^{16} allele had higher SBP (41)	SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg or antihypertensive therapy
55 pedigrees with ≥1 sib pair discordant for SBP and 589 nuclear families (2,523 individuals)	Caucasian Americans	5′LC(–19), C16, C27	Gly^{16} allele more common among HT compared to Arg^{16}; Glu^{27} allele more common among HT than Gln^{27} (49)	SBP > 140 mmHg, DBP > 90 mmHg and/or use of antihypertensive therapy
136 HT and 81 NT	African Caribbean	C16	Gly^{16} allele frequency was 0.85 in HT group compared to 0.66 in normotensive controls ($p < 0.001$) (43)	DBP > 95 mmHg or antihypertensive therapy
284 subjects from cross-sectional study	Swedes	C16 and C27	$Arg^{16}Gly$ heterozygotes had higher SBP (133.5 mmHg) compared with $Arg^{16}Arg$ (126 mmHg) and $Gly^{16}Gly$ (128.6) C27 had no influence on BP levels (44)	NA
842 HT and 633 NT	Japanese	C16, C27, 5′LC	No association between C16, 5′LC with BP level or HT phenotype; Glu^{27} allele was marginally more common in NT than HT subjects (47)	SBP ≥ 160 mmHg or DBP ≥ 95 mmHg
307 NT (128 black and 179 white) and 356 HT (155 black and 201 white)	Americans	C16, C27	NS difference in allele or genotype frequencies between HT and NT (48)	Administration of antihypertensive medication or SBP ≥ 140 mmHg or DBP ≥ 90 mmHg
76 HT and 167 NT	Caucasians and African Americans	C16	NS difference in allele or genotype frequencies between HT or NT; NS difference in any hemodynamic variables (59)	SBP > 140 mmHg or DBP > 95 mmHg
707 HT and 290 NT	French Caucasians	5′LC, C16, C27	NS difference in allele or genotype frequencies between HT and NT or with levels of BP (46)	DBP ≥ 105 mmHg without treatment or ≥ 100 mmHg with treatment

[a] Abbreviations: BP, blood pressure; C16, codon 16; C27, codon 27; DBP, diastolic blood pressure; DM, diabetes mellitus; 5′LC, 5′ leader cistron; HT, hypertension; NS, nonsignificant; NT, normotensive; OR, odds ratio; SBP, systolic blood pressure.

blood pressure and an additional 589 nuclear families (2,523) individuals. Among the genes studied, only polymorphisms in the β_2AR and the glutathione peroxidase 3 gene were associated with hypertension. For the β_2AR gene, the Gly^{16} allele was significantly more common among hypertensives than the Arg^{16} allele. Furthermore, the Glu^{27} allele was more common among hypertensives than Gln^{27} (49). In this study, the β_2AR polymorphisms accounted for 2% of the total variation in blood pressure, suggesting that interaction of several genetic loci contributes to the hypertension phenotype.

There are several possible explanations for the discordant findings in the β_2AR polymorphism hypertension studies. Among them are lack of statistical power, effects of other genetic loci linked to the SNP being investigated, differences in ethnic populations studied, and the lack of a standardized definition of phenotype. Two of these deserve special mention. First, there is no uniform phenotypic definition of hypertension throughout the candidate gene literature (Table IV). Clinically, patients are often classified with salt-sensitive hypertension, white-coat hypertension, or isolated systolic hypertension, to name a few, all of which are manifestations of different pathophysiologic processes. Thus, it seems likely that distinct genes contribute to these unique forms of hypertension. Second, based on the numerous conflicting results, codon 16 of the β_2AR may not be a causative hypertensive SNP. Instead, it is possible that certain ethnic populations (e.g., Scandinavians) may have a currently unidentified genetic polymorphism that is in LD with the Arg^{16} allele and is directly related to hypertension. Contrarily, other ethnic populations (e.g., African Americans, Japanese) may lack this variation linked with the Arg^{16} allele. As a result there would be a lack of an association with hypertension. Thus, it is imperative that future association studies with the β_2AR polymorphisms include an analysis by haplotype. However, disadvantages to studying haplotypes also exist. Ascertaining haplotypes increases the complexity of the study and also increases the sample size requirements. The variability in findings in the literature may not be surprising, given the issues described above and the fact that even if the β_2AR gene is a "hypertension gene," it probably contributes only minimally to hypertension. Ultimately, it seems clear that complex diseases such as hypertension will require a genomics approach to fully understand the genetic basis for the disease.

Heart Failure

In the nonfailing heart, the ratio of β_1:β_2 receptors is 80:20. However, in heart failure, the β_1AR down-regulates, and the ratio of β_1:β_2 receptors becomes 60:40 (50). Consequently, polymorphisms in the β_2AR gene may modify disease progression of patients with heart failure. Consistent with the data on the β_1AR polymorphisms, there were no differences in the β_2AR allele frequencies between patients with and without heart failure (51). Among patients with heart failure, the codon 16 and codon 27 polymorphisms were also not associated with prognosis. However, patients who carried the Ile^{164} allele were 4.8 times more likely (95% CI 2.0–11.5) to reach the composite endpoint of death or cardiac transplantation compared to Thr^{164} homozygotes (51). Despite these impressive results, this finding is based on only 10 patients with the Ile^{164} form; thus, replication in a larger population is required. An ostensible mechanism for the worsened prognosis could be the significantly lower peak myocardial oxygen consumption during maximal exercise among heart failure patients carrying the Ile^{164} allele compared with the Thr^{164} homozygotes (52). Thus, further work is needed, but it seems that β_2AR polymorphisms may influence prognosis in heart failure. Given the contribution of β_2 receptors in the failing heart, it is also possible that these polymorphisms could modify response to β-blocker therapy in heart failure patients.

Pharmacogenetics

Among the studies on the cardiovascular effects of β_2AR polymorphisms, the majority have investigated the response to β-adrenergic agonists among healthy volunteers. In general, these studies show that the Arg^{16} (45,53) and Glu^{27} homozygous genotypes (54) display enhanced vasodilation to β-adrenergic agonists. However, based on LD, the data from these two SNPs might be viewed as inconsistent because haplotype data suggest that the Arg^{16} and Glu^{27} only rarely occur on the same allele (55). Thus, it is more likely that patients carry the Arg^{16} and Gln^{27} on the same allele, highlighting the importance of haplotype analyses in studies involving the β_2AR. In perhaps the best study to date in this area, an *in vivo* study showed that the Arg^{16} and Gln^{27} forms exhibit enhanced agonist-mediated desensitization to the β_2-agonist vasodilatory response. Moreover, Gly16 homozygotes (irrespective of the codon 27 polymorphism) were resistant to agonist-mediated desensitization (56). This study is important because the investigators evaluated more than one polymorphism of the β_2AR, and thus, the effects of haplotype can be assessed.

There has also been a small study of the *in vivo* consequences of the codon 164 polymorphisms relative to agonist-mediated response, which include six carriers of Ile^{164} and 12 Thr^{164} homozygotes (57). The results demonstrated that healthy subjects with the Ile^{164} allele had impaired terbutaline-induced increases in heart rate and contractility, but blood pressure responses to terbutaline were not different by genotype. These findings could be considered consistent with the findings of worsened prognosis and reduced myocardial oxygen consumption among patients with heart failure (51,52).

Although these studies add insight into the functional consequences of the β_2AR genetic polymorphisms, they provide little insight into the impact of these polymorphisms in drugs used to treat cardiovascular disease. For example, β_2AR polymorphisms might contribute to variability in the response to β-blockers, particularly in heart failure, where the contribution of β_2AR blockade to the β-blocker benefit remains controversial. β_2AR polymorphisms could also contribute to variability in response to β-agonists used in support of the failing heart. However, given the relative importance of the β_1ARs vs. β_2ARs in the cardiovascular system, it seems likely that the β_2AR genetic polymorphisms will have a secondary role, if any, to the β_1AR polymorphisms in describing variable drug response for drugs acting at the βARs. Nonetheless, experimental approaches that consider the influence of variability in multiple genes are likely to be more informative than analysis of single genes alone. Thus, it is imperative that pharmacogenetic studies of β-blockers or β-agonists include polymorphisms not just in the β_1AR gene but in other genes that may also be linked to response, such as β_2AR, $G_{s\alpha}$, and others.

SUMMARY

In some respects, the literature on the influence of βAR genetic polymorphisms on cardiovascular disease and pharmacogenetics is in its infancy. There is little doubt that both the β_1AR and β_2AR genes have nonsynonymous genetic polymorphisms that have functional significance. What remains to be uncovered is a better understanding of the relationship between these genetic polymorphisms and cardiovascular disease. For those with a pharmacology or pharmacy focus, the issue of even greater interest is the impact of these genetic polymorphisms on response to drugs that act at the βARs. There is little doubt that the next 5 years will see a marked increase in our understanding of these issues. Ultimately, knowledge of a person's βAR genotypes may lead to improvements in the understanding and treatment of their cardiovascular disease.

ACKNOWLEDGMENTS

This work was supported in part by grants R01 HL64691, R01 HL64924, K24 HL68834, R03 HL65729, and U01 HL69758 from the National Institutes of Health.

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